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TAK1: Another mesh in the NF-κB – JNK controlled network causing hepatocellular carcinoma

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COMMENTARY ON:

TAK1 suppresses a NEMO-dependent but NF-kappab-independent pathway to liver cancer. Kira Bettermann, Mihael Vucur, Johannes Haybaeck, Christiane Koppe, Jörn Janssen, Felix Heymann, Achim Weber, Ralf Weiskirchen, Christian Liedtke, Nikolaus Gassler, Michael Müller, Rita de Vos, Monika Julia Wolf, Yannick Boege, Gitta Maria Seleznik, Nicolas Zeller, Daniel Erny, Thomas Fuchs, Stefan Zoller, Stefano Cairo, Marie-Annick Buendia, Marco Prinz, Shizuo Akira, Frank Tacke, Mathias Heikenwalder, Christian Trautwein, Tom Luedde. Cancer Cell. 2010 May 18;17(5):481–96. Copyright (2010). Abstract reprinted with permission from Elsevier.

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Abstract: *The MAP3-kinase TGF-beta-activated kinase 1 (TAK1) critically modulates innate and adaptive immune responses and connects cytokine stimulation with activation of inflammatory signaling pathways. Here, we report that conditional ablation of TAK1 in liver parenchymal cells (hepatocytes and cholangiocytes) causes hepatocyte dysplasia and early-onset of hepatocarcinogenesis, coinciding with biliary ductopenia and cholestasis. TAK1-mediated cancer suppression is exerted through activating NF-kappaB in response to tumor necrosis factor (TNF) and through preventing Caspase-3-dependent hepatocyte and cholangiocyte apoptosis. Moreover, TAK1 suppresses a procarcinogenic and pronecrotic pathway, which depends on NF-kappaB-independent functions of the I kappaB-kinase (IKK)-subunit NF-kappaB essential modulator (NEMO). Therefore, TAK1 serves as a gatekeeper for a protumorigenic, NF-kappaB-independent function of NEMO in parenchymal liver cells.*

Hepatocellular cancer (HCC) is the fifth most common cancer yet the third most common cause of cancer related death with a 5-year survival rate of just below 10% [1]. Viral infections, obesity, or alcohol abuse trigger chronic liver damage leading to inflammation and fibrosis and thus substantially increase the risk to develop HCC [2]. Using complex genetic mouse models, several key signaling cascades causing inflammation and fibrosis have been identified in recent years helping to improve our understanding of the exact underlying molecular mechanisms of these processes.

One important player in both inflammation and cancer is the transcription factor NF-κB [3]. Classical NF-κB activation is controlled by the multi-protein complex IκB-kinase, which is comprised of the two catalytical subunits IKKα and IKKβ as well as the regulatory subunit IKKγ (NEMO). IKKβ-dependent NF-κB activation is considered to provide pro-tumorigenic properties by suppressing cell death in tumor cells in a cell autonomous manner and by production of pro-inflammatory, pro-proliferative factors in myeloid cells that can act on tumor cells in a paracrine fashion [4]. However, during the pathogenesis of HCC, NF-κB's particular importance for hepatocyte survival may confer a liver-specific anti-tumorigenic function [5]. Because of the regenerative capacity of the liver, enhanced hepatocyte apoptosis caused by the loss of NF-κB function results in a stronger c-Jun N-terminal kinase (JNK) dependent compensatory proliferative response and ultimately in a higher tumor load. This was documented both in a model of diethylnitrosamine (DEN) induced HCC in the case of liver specific IKKβ-deficiency [6] as well as in mice with a hepatocyte restricted loss of IKKγ, that even spontaneously developed HCC [7]. It was suggested that, in the case of NF-κB deficiency, transcription of anti-oxidant scavengers was suppressed causing an accumulation of reactive oxygen species (ROS) which in turn led to the inhibition of MAP kinase phosphatases (MKPs) and ultimately to the sustained activation of JNK [8]. Accordingly, treatment with an anti-oxidant or genetic ablation of JNK1 reversed the increased susceptibility to DEN-induced HCC in NF-κB deficient animals [6,7,9].

Now another player has entered the complex field of NF-κB/JNK interaction in the pathogenesis of HCC: transforming growth factor (TGF) β-activated kinase 1 (TAK1). TAK1 belongs to the mitogen-activated protein kinase kinase kinase (MAP3K) family and is activated by various inflammatory mediators including TNFα, IL-1 as well as LPS. TAK1 is involved in the stimulation of the IKK complex as well as JNK and p38 [10].

In a study recently published in *Cancer Cell*, Bettermann *et al.* addressed the function of TAK1 in HCC development [11]. Loss of TAK1 in liver parenchymal cells led to spontaneous hepatitis, hepatocyte dysplasia, liver fibrosis, and spontaneous death of the animals within 40 weeks. Importantly, almost 90% of the mice had developed true HCCs characterized by marked chromosomal aberrations and the expression of both α-fetoprotein as

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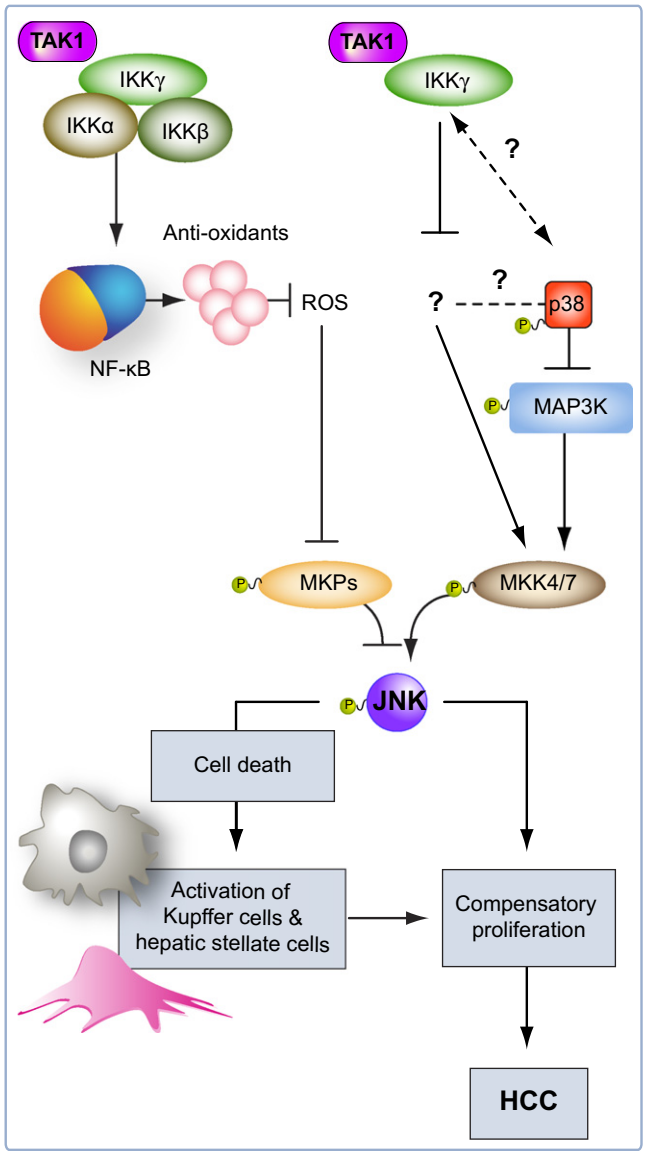

Fig. 1. TAK1 and IKKγ control two different pathways that ultimately prevent JNK activation. The first one depends on NF-κB and leads to the transcription of genes encoding anti-oxidant proteins that suppress ROS accumulation. Therefore, MAP kinase phosphatases can terminate JNK activation. In case of IKKβ or IKKγ loss, ROS block MKPs, which leads to sustained JNK activation and increased cell death and thereby to the release of pro-inflammatory cytokines, such as IL-1α, which activate adjacent Kupffer cells to secrete pro-inflammatory and mitogenic products that stimulate a compensatory hyperproliferation. Now, Bettermann and colleagues demonstrated that TAK1 can also suppress MKK4 and MMK7 and thereby JNK activity. Surprisingly, IKKγ is an essential component in this cascade. However, in case of TAK1 deficiency, JNK activation is higher and tissue damage is stronger and consequently HCC development more rapid in comparison to mice with hepatocyte restricted IKKγ-deletion. Nevertheless, concomitant loss of TAK1 and IKKγ in hepatocytes suppressed elevated MKK4/MKK7-JNK signaling observed in TAK1 single knockout cells thus clearly supporting an IKKγ-mediated function independently of NF-κB signaling. Which the additional players in this cascade are or what the role of p38 is, remains to be analyzed.

well as H19. Similar findings were also reported by Inokuchi *et al.* in an independently conducted study [12]. Both groups suggested hepatocyte death, consecutive inflammation, and compensatory proliferation associated with elevated JNK activation as the underlying cause for HCC development in TAK1-deficient livers. This strongly resembled the phenotype observed in mice with a hepatocyte-restricted loss of NF-κB.

However, Bettermann and colleagues suggested that, unlike in NF-κB deficient hepatocytes, in TAK1-deficient livers JNK activation was dependent on the increased phosphorylation of MKK4 and MKK7. Accordingly, nevertheless very surprisingly, compound mutants with concomitant loss of IKKγ and TAK1 in the liver parenchymal cells, decreased MKK4/MKK7 and JNK activation and prevented necrosis, dysplasia, and most importantly HCC development, when double mutant mice were monitored up to 50 weeks. Thus, while in a TAK1 proficient background IKKγ acts as a NF-κB dependent tumor suppressor, its role switches to a NF-κB independent tumor promoter once TAK1 function is ablated. Thus, these results clearly demonstrate for the first time, functionally, a NF-κB independent function of IKKγ that is extremely relevant for the pathogenesis of HCC. The fact that IKKγ is involved in the regulation of other NF-κB independent signaling pathways may also help to explain previous findings in mice with a cell specific deletion of IKKγ that had not been observed when IKKβ was absent [6,7] (Fig. 1).

However, the exact underlying molecular mechanisms linking TAK1/IKKγ to MKK4/MKK7 regulation still remain to be elucidated. Considering that also hepatocyte specific loss of p38 is associated with increased phosphorylation of MKK4 and MKK7, elevated JNK activation and HCC development [13] it may also be interesting to address whether this MAP kinase is involved in this interplay. It will be essential to fully understand the cell autonomous complex interaction of various inflammatory and stress signaling pathways, which is further influenced by paracrine effects mediated by Kupffer cells and hepatic stellate cells in the vicious cycle of hepatocyte death, Kupffer cell activation and subsequent compensatory hyperproliferation. Importantly, in contrast to DEN-induced hepatic tumors, TAK1 deficient HCC develop in the context of liver fibrosis, as it is commonly found in human HCC. The current results by Bettermann *et al.* open, therefore, a completely new avenue and promise very exciting results that are still lying ahead of us. Thus, these new findings comprise a very important step on the long way to discover urgently needed new therapeutic targets and effective therapy regimens for this deadly disease.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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